

WHAT IS CLAIMED IS:

1           1.       A method of making probe chips comprising the steps of:  
2           forming a plurality of probe arrays on a substrate;  
3           separating said substrate into a plurality of chips, each of said chips comprising at  
4   least one probe array thereon; and  
5           mating at least one of said chips to a package, said package comprising a reaction  
6   chamber, said reaction chamber comprising inlets for flowing fluid therein, said at least one  
7   probe array in fluid communication with said reaction chamber.

1           2.       The method as recited in claim 1 wherein said package is made by the steps  
2   of:  
3           injection molding first and second halves of said package; and  
4           mating said first and second halves together.

1           3.       The method as recited in claim 2 wherein one of said halves comprises flow  
2   channels therein, said flow channels in communication with said inlets.

1           4.       The method as recited in claim 3 further comprising the step of applying a  
2   reenterable seal to flow channels in said package.

1           5.       The method as recited in claim 1 wherein said substrate comprises alignment  
2   marks for forming said probe arrays thereon in a desired position, and wherein said  
3   alignment marks are used to identify locations for said separating of said substrate into chips.

1           6.       The method as recited in claim 1 wherein said package comprises an  
2   alignment structure thereon, wherein said step of mating said chip to said package uses said  
3   alignment structures to position said package at a desired position.

1           7.       The method as recited in claim 1 wherein said package comprises an  
2   alignment structure thereon, and further comprising the step of identifying the location of at  
3   least one target on said probe array in a scanner, wherein said package is placed at a desired  
4   location in said scanner using said alignment structure.

1           8.     The method as recited in claim 1 wherein said step of forming a plurality of  
2 probe arrays comprises the steps of:  
3           selectively exposing said substrate to light;  
4           coupling selected monomers to said substrate where said substrate has been exposed  
5 to light.

1           9.     The method as recited in claim 1 wherein said step of separating comprises  
2 the steps of:  
3           scribing said substrate in desired locations;  
4           breaking said substrate along said scribe lines.

1           10.    The method as recited in claim 1 wherein said step of forming a plurality of  
2 probe arrays on said substrate is a step of forming a plurality of oligonucleotide probe arrays  
3 on said substrate.

1           11.    The method as recited in claim 10 further comprising the steps of flowing  
2 labeled oligonucleotide target molecules through said reaction chamber and identifying  
3 where said target molecules have bound to said substrate.

1           12.    The method as recited in claim 11 wherein said package comprises a  
2 temperature probe and further comprising the step of monitoring and adjusting a temperature  
3 in said reaction chamber.

1           13.    The method as recited in claim 1 wherein said package is formed by the steps  
2 of:  
3           forming first and second package portions; and  
4           acoustically welding said first and second package portions together.

1           14.    The method as recited in claim 1 wherein said step of mating said chips to  
2 packages comprises the step of binding said chips to said package with an adhesive.

1           15.    The method as recited in claim 14 wherein said packages comprise a recessed  
2 region thereon, whereby said chips do not extend above a surface of said packages.

1           16.     The method as recited in claim 1 further comprising the step of flowing target  
2 molecules through said reaction chamber.-

1           17.     An apparatus for packaging a substrate, said apparatus comprising:  
2           a substrate having a first surface and a second surface, said first surface comprising a  
3 probe array;  
4           a body having a mounting surface with a fluid cavity, said second surface attached to  
5 said cavity; and  
6           a cover attached to said mounting surface for sealing said cavity.

1           18.     The apparatus of claim 17 wherein said cavity comprises an inlet port and an  
2 outlet port, said inlet and outlet ports permitting fluids to circulate into and through said  
3 cavity.

1           19.     The apparatus of claim 18 wherein said inlet and outlet ports comprise a  
2 reenterable seal.

1           20.     The apparatus of claim 17 wherein said probe array comprises an array of  
2 oligonucleotide probes.

1           21.     An apparatus for packaging a substrate, said apparatus comprising:  
2           a substrate having a first surface and a second surface, said first surface comprising a  
3 probe array and said second surface being an outer periphery of said first surface;  
4           a body having a mounting surface, an upper surface, and a cavity bounded by said  
5 mounting surface and said upper surface, said second surface being attached to said cavity  
6 and said first surface being within said cavity; and  
7           a cover attached to said mounting surface for defining an upper boundary to said  
8 cavity;  
9           wherein said cavity comprises a diffuser and a concentrator, said diffuser and said  
10 concentrator permitting laminar fluid flow through said cavity.

1           22.     The apparatus of claim 21 wherein said probe array comprises an array of  
2 oligonucleotide probes.

1           23.     The apparatus of claim 21 wherein said cover comprises a depression for  
2 receiving a temperature control element to maintain a reaction temperature in said cavity.

1           24.     The apparatus of claim 21 wherein said cover comprises a first half mated to a  
2 second half.

1           25.     The apparatus of claim 24 wherein said first half comprises a first channel and  
2 a second channel, said first channel being in fluid communication with said diffuser and said  
3 second channel being in fluid communication with said concentrator.

1           26.     The apparatus of claim 25 wherein said second half comprises a third channel  
2 and a fourth channel, said third channel being in fluid communication with said first channel,  
3 and said fourth channel being in fluid communication with said second channel. .

1           27.     The apparatus of claim 26 wherein said first channel and said second channel  
2 comprise re-enterable seals for sealing fluid in said cavity.

1           28. An apparatus for mixing a fluid, the apparatus comprising:  
2           a first substrate comprising a first inner surface functionalized with a microarray of  
3 reactive moieties;  
4           a substantially parallel second substrate also comprising a second inner surface,  
5 wherein said first and second inner surfaces bound a closed chamber there between, said  
6 chamber adapted to retain a quantity of fluid so that the fluid is in contact with both surfaces;  
7           at least one bubble disposed within said chamber; and  
8           means for moving the chamber so that the bubble moves relative to the fluid to effect  
9 mixing of the fluid.

1           29. An apparatus for mixing a fluid, the apparatus comprising:  
2           a first substrate comprising a first inner surface functionalized with a microarray of  
3 reactive moieties;  
4           a substantially parallel second substrate also comprising a second inner surface,  
5 wherein said first and second inner surfaces bound a closed chamber there between, said  
6 chamber adapted to retain a quantity of fluid so that the fluid is in contact with both surfaces;  
7           at least one bubble disposed within said chamber, wherein said bubble is a magnetic

8 particle; and  
9 means for moving the bubble relative to the fluid to effect mixing of the fluid.  
1 30. The apparatus of claim 28, wherein the closed chamber has a thickness of less  
2 than about 2 millimeters.  
1 31. The apparatus of claim 29, wherein the closed chamber has a thickness of less  
2 than about 2 millimeters.  
1 32. The apparatus of claim 28, wherein both inner surfaces are functionalized with  
2 reactive moieties.  
1 33. The apparatus of claim 29, wherein both inner surfaces are functionalized with  
2 reactive moieties.  
1 34. The apparatus of claim 28, wherein the bubble comprises a gas.  
1 35. The apparatus of claim 28, wherein the bubble comprises nitrogen.  
1 36. The apparatus of claim 29, wherein said magnetic particle is a magnetic bead.  
1 37. The apparatus of claim 28, wherein the bubble is produced by introducing a  
2 volume of the fluid that is less than the total volume of the closed chamber.  
1 38. The apparatus of claim 28, further including a flexible seal between the inner  
2 surface of the first substrate and the inner surface of the second substrate.  
1 39. The apparatus of claim 38, wherein said flexible seal includes a gasket.  
1 40. The apparatus of claim 29, further including a flexible seal between the inner  
2 surface of the first substrate and the inner surface of the second substrate.  
1 41. The apparatus of claim 40, wherein said flexible seal includes a gasket.  
1 42. The apparatus of claim 28, further comprising means for introducing fluid into  
2 the closed chamber.  
1 43. The apparatus of claim 29, further comprising means for introducing fluid into  
2 the closed chamber.  
1 44. The apparatus of claim 28, wherein the first substrate and the second substrate  
2 are individually comprised of a material selected from the group consisting of glass, silicon,  
3 fused silica, plastic, and a combination thereof.  
1 45. The apparatus of claim 29, wherein the first substrate and the second substrate  
2 are individually comprised of a material selected from the group consisting of glass, silicon,  
3 fused silica, plastic, and a combination thereof.  
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- 1        46. The apparatus of claim 28, wherein the first substrate is comprised of glass.
- 1        47. The apparatus of claim 29, wherein the first substrate is comprised of glass.
- 1        48. The apparatus of claim 28, wherein the means for moving the bubble is selected  
2 from the group consisting of rotating the apparatus about an axis, rolling the apparatus, and  
3 reciprocally shaking the apparatus.
- 1        49. A method for mixing a fluid, comprising:  
2 providing an apparatus according to claim 28;  
3 introducing a fluid into the closed chamber;  
4 introducing a bubble within the fluid; and  
5 moving the bubble in the fluid to effect mixing of the fluid.
- 1        50. A method for mixing a fluid, comprising:  
2 providing an apparatus according to claim 29;  
3 introducing a fluid into the closed chamber;  
4 introducing a bubble within the fluid; and  
5 moving the bubble in the fluid to effect mixing of the fluid.
- 1        51. A method for mixing a fluid, comprising:  
2 providing an apparatus according to claim 30;  
3 introducing a fluid into the closed chamber,  
4 introducing a bubble within the fluid; and  
5 moving the bubble in the fluid to effect mixing of the fluid.
- 1        52. A method for mixing a fluid, comprising:  
2 providing an apparatus according to claim 31;  
3 introducing a fluid into the closed chamber;  
4 introducing a bubble within the fluid; and  
5 moving the bubble in the fluid to effect mixing of the fluid.
- 1        53. A method for mixing a fluid, comprising:  
2 providing an apparatus according to claim 36;  
3 introducing a fluid into the closed chamber;  
4 introducing a bubble within the fluid; and  
5 moving the bubble in the fluid to effect mixing of the fluid.

1        54. A method for mixing a fluid, comprising:  
2        providing an apparatus according to claim 48;  
3        introducing a fluid into the closed chamber;  
4        introducing a bubble within the fluid; and  
5        moving the bubble in the fluid to effect mixing of the fluid.

1        55. An apparatus for mixing a fluid, comprising:  
2        a first substrate and a second substrate having inner surfaces that define a closed  
3        chamber therebetween, said chamber adapted to retain a quantity of fluid so that the fluid is  
4        in contact with both inner surfaces;  
5        means for creating bubbles in the fluid within the apparatus, whereby each bubble  
6        displaces the fluid resulting in mixing; and  
7        means for moving a bubble in the fluid.

1        56. The apparatus of claim 55, wherein the first substrate comprises a material  
2        selected from the group consisting of glass, silicon, fused silica, and plastic.

1        57. An apparatus for mixing a fluid, comprising:  
2        a first substrate and a substantially parallel second substrate having inner surfaces that  
3        define a closed chamber therebetween, said chamber adapted to retain a quantity of fluid so  
4        that the fluid is in contact with both inner surfaces;  
5        means for providing bubbles in the fluid within the apparatus, whereby each said  
6        bubble displaces the fluid resulting in mixing; and  
7        means for moving a bubble in the fluid.

1        58. An apparatus for mixing a fluid, comprising:  
2        a first substrate and a second substrate having inner surfaces that define a closed  
3        chamber therebetween, said chamber adapted to retain a quantity of fluid so that the fluid is  
4        in contact with both inner surfaces; and  
5        means for creating bubbles in the fluid at selected locations within the apparatus,  
6        whereby each bubble displaces the fluid resulting in mixing; and wherein at least one of said  
7        inner surfaces is functionalized with reactive moieties.

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1           59. The apparatus of claim 58 wherein the reactive moieties comprise monomeric  
2 species covalently bound to said inner surface, each of the monomeric species having at least  
3 one reactive site.

1           60. The apparatus of claim 59 wherein the monomeric species are nucleotides.

1           61. The apparatus of claim 60 wherein the monomeric species are amino acids.

1           62. The apparatus of claim 61 wherein the reactive moieties comprise reactive sites  
2 of monomeric species present at the terminus of a surface-bound polymer.

1           63. The apparatus of claim 62 wherein the surface-bound polymer comprises a  
2 polynucleotide.

1           64. The apparatus of claim 62 wherein the surface-bound polymer comprises a  
2 polyribonucleotide.

1           65. The apparatus of claim 64, wherein the surface-bound polymer comprises a  
2 polypeptide.

1           66. A method comprising:

2           providing a first substrate and a second substrate having inner surfaces that define a  
3 closed chamber therebetween, said chamber adapted to retain a quantity of fluid so that the  
4 fluid is in contact with both inner surfaces, and wherein at least one of said inner surfaces is  
5 functionalized with polynucleotides, polypeptides, or polysaccharides;

6           introducing a fluid containing a plurality of components into the closed chamber so as  
7 to provide a quantity of fluid therein in contact with both inner surfaces;

8           providing a bubble in the fluid; and

9           moving a bubble within the fluid to result in mixing.

1           67. A method according to claim 66, wherein the polynucleotide is a  
2 polyribonucleotide.

1           68. A method according to claim 66, wherein the chamber is adapted to retain a film  
2 of fluid in contact with both inner surfaces.

1           69. A method according to claim 66 wherein the inner surfaces of the first and  
2 second substrates are substantially parallel.

1           70. A method according to claim 66, wherein the chamber is less than two  
2 millimeters in thickness.

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- 1           71. A method according to claim 66 further including using heat for said mixing.
- 1           72. A method according to claim 66 further including using ultrasonic radiation for  
2 said mixing.
- 1           73. A method of claim 66, wherein the at least one of said inner surfaces is  
2 functionalized with polynucleotides.
- 1           74. A method of 66, wherein the at least one of said inner surfaces is functionalized  
2 with polypeptides.
- 1           75. A method comprising:  
2           providing a first substrate and a second substrate having inner surfaces that define a  
3 closed chamber therebetween, said chamber adapted to retain a quantity of fluid so that the  
4 fluid is in contact with both inner surfaces, and wherein at least one of said inner surfaces is  
5 functionalized with an array of RNA or DNA probes;  
6           introducing a fluid sample containing DNA or RNA into the closed chamber so as to  
7 provide a quantity of fluid therein in contact with both inner surfaces;  
8           providing a bubble in the fluid;  
9           moving a bubble within the fluid to result in mixing;  
10          after hybridization is complete, removing the sample from the apparatus; and  
11          analyzing the functionalized inner surface for DNA or RNA that has hybridized.
- 1           76. A method according to claim 75 additionally comprising heating the DNA or  
2 RNA containing sample fluid while in the closed chamber.
- 1           77. A method according to claim 76 additionally comprising washing the  
2 functionalized inner surface prior to the analyzing.
- 1           78. A method according to claim 75, wherein the bubble is moved in a circular  
2 pattern.
- 1           79. A method according to claim 78, wherein the bubble is moved in the circular  
2 pattern that includes exiting the closed chamber.
- 1           80. A method comprising:  
2           providing a first substrate and a second substrate having inner surfaces that define a  
3 closed chamber therebetween, said chamber adapted to retain a quantity of fluid so that the  
4 fluid is in contact with both inner surfaces, and wherein at least one of said inner surfaces is  
5 functionalized with an immobilized biological polymer;

6       introducing a fluid containing a plurality of components into the closed chamber so as  
7       to provide a quantity of fluid therein in contact with both inner surfaces;  
8       providing a bubble in the fluid; and  
9       moving a bubble within the fluid to result in mixing.

1       81. A method according to claim 80, wherein said biological polymer includes a  
2       polynucleotide.

1       82. A method according to claim 81, wherein said polynucleotide is a  
2       polyribonucleotide.

1       83. A method according to claim 80, wherein said biological polymer includes  
2       polypeptides.

1       84. A method according to claim 80, wherein said biological polymer includes  
2       polysaccharides.

1       85. A method for mixing a film of fluid, comprising:  
2       providing a first substrate and a substantially parallel second substrate having inner  
3       surfaces that define a closed chamber therebetween, said chamber adapted to retain a quantity  
4       of fluid so that the fluid is in contact with both inner surfaces;  
5       introducing a fluid containing a plurality of components into the closed chamber so as  
6       to provide a film of fluid therein; and  
7       nucleating a bubble within the film of fluid, whereby, as the bubble is nucleated and  
8       dispelled, the fluid is displaced resulting in mixing.

1       86. The method of claim 85, wherein the dispelling comprises moving the bubble.

1       87. An apparatus for mixing a fluid, comprising:  
2       a first substrate and a second substrate having inner surfaces that define a closed  
3       chamber therebetween, said chamber adapted to retain a quantity of fluid so that the fluid is  
4       in contact with both inner surfaces;

5       means for nucleating bubbles in the fluid comprising discrete sources for creating  
6       individual bubbles at selected locations within the apparatus, whereby, as each bubble is  
7       nucleated and dispelled, the fluid is displaced resulting in mixing; and

8       means for moving a bubble in the fluid.

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